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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZHOU, SHUBO	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,062	BRUCE ET AL.	
	Examiner	Art Unit	
	SHUBO (Joe) ZHOU	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21 and 38-56* is/are pending in the application.

4a) Of the above claim(s) *20,21,38-41 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RCE

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission including amendment to the claims filed on 4/28/10 has been entered.

Status of the Claims

Claims 20-21, and 38-56 are presently pending.

Claims 1-19, 22-37, and 57 have been canceled.

Claims 20-21, 38-41 and 56 have been previously withdrawn, and remain withdrawn, from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 42-55 are under consideration.

Claim Rejections-35 USC § 112

The rejection of claims 42-55 under 35 U.S.C. 112 , second paragraph, set forth in the previous Office action is withdrawn in view of applicant's amendment filed 4/28/10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 42-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Charles et al. (IDS document: WO 01/07651 A2, 1 February 2001) in view of Haselbeck et al. (IDS document: WO 01/70955 A2, 27 September 2001).

In view of the indefiniteness of the claims as set forth above, the references cited are being applied to the best interpretation of the claims as currently written.

The claims are drawn to a method for identifying a library of putative essential or important genes using a High Throughput Transposon Insertion Map (HTTIM) database, comprising: mutagenizing a Staphylococcus genome with a transposon such that individual cells each containing at least one transposon insertion site are isolated; collecting and mapping the polynucleotide sequences of the transposon insertion sites in each individual cell so as to form a database of polynucleotide sequences of the transposon insertion sites, or an HTTIM; comparing the polynucleotide sequences of transposon insertion sites with the Staphylococcus genomic sequence to identify open reading frames in the genome that are not disrupted by a transposon insertion; and forming a library from said putative essential or important genes that are not disrupted by a transposon.

Charles et al. disclose a method for making a library of putative essential genes comprising mutagenizing bacterial cells such as Staphylococcus genome with transposon to obtain a library of mutants; and isolating polynucleotide sequences from the library which flank the inserted transposon sites to obtain a pool of consensus probes. These steps are interpreted as the "mutagenizing" and the "collecting" steps recited in the instant claims. The method of Charles et al. also includes hybridizing the consensus probes with a polynucleotide library from the same organism, and identifying nucleotide sequences in the library to which the consensus probe sequences do not hybridize, which are putative essential genes of the organism. See at least pages 2 and 6-7. One having ordinary skill in the art would recognize that since the consensus sequences are those

flanking the transposons, they represent those genes that are disrupted by the transposons, and that those sequences from the library that are identified as not being hybridized to the consensus sequences are those genes that are not disrupted by any transposons. Charles et al. also disclose that ideally the hybridization is done with the library in the form of a gridded array that represents the whole genome of the organism and each location represents a single open reading frame. When the entire genomic sequence is known, the order of all the open reading frames is known and the transposon sites are thus mapped by the hybridization. See at least pages 13-14. This hybridization step is interpreted as comparing a pool of sequences of the insertion sites (interpreted as a file of sequences of insertion sites) with a library of genomic sequences of the organism.

Charles et al. do not explicitly disclose comparing the polynucleotide sequences of transposon insertion sites with the genomic sequence of the organism. However, as set forth above, Charles et al. do teach hybridizing the consensus probes with a polynucleotide library from the same organism, and identifying nucleotide sequences in the library to which the consensus probe sequences do not hybridize, which are putative essential genes of the organism. One of ordinary skill in the art would have understood that the physical hybridization between two sequences by Charles et al. would conceivably be considered as comparison between the two sequences because the result of the hybridization, i.e. sequences that match and mismatch would be similar to the result of a comparison, i.e. an alignment showing sequences that match and mismatch.

It would have been obvious to one having ordinary skill in the art that computational comparisons with a computer program, which would have been readily available in the art, would have been much more time and cost saving than using

experimental hybridization. Therefore, one having ordinary skill in the art would have been motivated to modify the method of Charles et al. to apply a computational comparison mean between the sequences of the consensus probes and the genomic sequence of the same organism. There would have been a reasonable expectation of success because obtaining the polynucleotide sequences from the library of consensus probes would have been routine as there would have been routine high throughput sequencing techniques available in the art and the entire genomic sequence of Staphylococcus would have been available in the art.

Additionally, Haselbeck et al. disclose a method for identifying putative essential genes by using antisense sequences. The method comprises identifying nucleotide sequences from the inserts of vectors that represent sequences of genes affecting proliferation and growth, comparing the sequences with know genomic sequences of the organism in databases such as GenBank, TIGR databases and the Pathoseq database to identify open reading frames that comprise these sequences, which are genes affecting proliferation and growth. See at least pages 94-96.

It would have been obvious to one of ordinary skill in the art at the time of the invention that the way of comparing isolated sequences with known databases containing entire genomic sequences and/or all open reading frames to identify genes or open reading frames as disclosed by Haselbeck et al., would be much more advantageous, such as time saving, than the physical hybridization method as disclosed by Charles et al. Therefore, one of ordinary skill in the art at the time of the instant invention was made would have been motivated by Haselbeck et al. to modify the method of Charles et al. to applying the method of comparing a database of sequences of insertion sites with a

database containing the entire genomic sequence and all the open reading frames of the organism to take advantage of the latter method such as to save time.

Again, there would have been a reasonable expectation of success because obtaining the polynucleotide sequences from the library of consensus probes would have been routine as there would have been routine high throughput sequencing techniques available in the art and the entire genomic sequence of Staphylococcus would have been available in the art.

With regard to claims 45-50, which specify the approximate numbers of transposons in the mutant library and number of genes in the library of putative essential genes, it would have been obvious to one of ordinary skill in the art that the number of transposons in the mutant library and the number of essential genes as disclosed by Charles would vary depending on the scale and exhaustiveness of the particular experiment and the genome size of the organisms up to the maximum number of essential genes, and the extend of the identification. Charles et al. encourage combining two transposon libraries thereby increasing the probability of obtaining transposon insertions in a greater number of genes. See page 9. It would have been obvious that one could obtain any number of transposons or genes in the library as desired.

With regard to claim 51, which recite statistical calculations, given that Charles et al. and Haselbeck et al. teach of using bioinformatics tools including searching databases of GenBank etc. using BLAST and database comparison, it would have been readily apparent that certain statistical calculations such as probability would be applied.

With regard to claims 53-55, which recite verifying the essential genes, Charles et al. disclose a method of such verification involving creating promoter swap mutants. See pages 16-17.

Applicant's arguments filed 4/28/10 have been fully considered but they are not persuasive. Applicant argues that the cite references do not suggest forming a database of polynucleotide sequences of transposon insertion sites and comparing these sequences with Staphylococcus genomic sequence. This is unpersuasive because as set forth in the previous Office action and reiterated above, one of ordinary skill in the art would have understood that the physical hybridization between two sequences by Charles et al. would conceivably be considered as comparison between the two sequences because the result of the hybridization, i.e. sequences that match and mismatch would be similar to the result of a comparison, i.e. an alignment showing sequences that match and mismatch.

It would have been obvious to one having ordinary skill in the art that computational comparisons with a computer program, which would have been readily available in the art, would have been much more time and cost saving than using experimental hybridization. Therefore, one having ordinary skill in the art would have been motivated to modify the method of Charles et al. to apply a computational comparison mean between the sequences of the consensus probes and the genomic sequence of the same organism. There would have been a reasonable expectation of success because obtaining the polynucleotide sequences from the library of consensus probes would have been routine as there would have been routine high throughput sequencing techniques available in the art and the entire genomic sequence of Staphylococcus would have been available in the art.

With regard to applicant's assertion that Charles et al. do not sequence the transposon insertion sites, as set forth in the previous Office action, Charles et al. on page 2, lines 16-17, explicitly disclose isolating polynucleotide sequences from the library which flank the inserted transposons. One having ordinary skill in the art would understand that the site of transposon insertion is a relative term in that the sequences flanking the transposon are parts of the "site" where transposons inserted, and thus this collection of polynucleotide sequences flanking the inserted transposons by Charles et al. are interpreted as the polynucleotide sequences of the transposon insertion sites of the instant claims.

Examiner's Special Note: Since this is a rejection after the filing of an RCE, applicant is encouraged to conduct an interview with the examiner if such interview is believed to clarify any potential confusions and misunderstanding, and find ways to amend the claims to overcome the rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shubo (Joe) Zhou, whose telephone number is 571-272-0724. The examiner can normally be reached Monday-Friday from 8 A.M. to 4 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran, can be reached on 571-272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Shubo (Joe) Zhou/

SHUBO (JOE) ZHOU, PH.D.

PRIMARY EXAMINER